National Institute of Environmental Health Sciences

Workshop: Can Nutrition Modify the Impact of Environmental Exposures on Autism Spectrum Disorder?

Brought to you by the Division of Extramural Research and Training Autism Program

June 21–22, 2022

National Institutes of Health • U.S. Department of Health and Human Services

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Workshop: Can Nutrition Modify the Impact of Environmental Exposures on Autism Spectrum Disorder?

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Daniel Geschwind, *University of California, Los Angeles*

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Jorge Chavarro, *Harvard T.H. Chan School of Public Health*

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2:40 – 3:55 p.m. **Panel Discussion: Opportunities, Challenges, and Implications. Where Do We Go From Here?**

Youssef Oulhote, *University of Massachusetts, Amherst*

Jose Cordero, *University of Georgia*

Julie Daniels, *University of North Carolina at Chapel Hill*

Rosalind Wright, *Icahn School of Medicine at Mount Sinai*

Andres Cardenas, *University of California, Berkeley*

Kimberly Gray, *NIEHS (Moderator)*

3:55 – 4:00 p.m. **Adjournment**
Cindy Lawler, *NIEHS*

Presenter Biographies

DAN GESCHWIND

Dan Geschwind, M.D., Ph.D., is the Gordon and Virginia MacDonald Distinguished Professor of Neurology, Psychiatry, and Human Genetics at UCLA. In his capacity as senior associate dean and associate vice chancellor of precision health, he leads the Institute for Precision Health at UCLA. In his laboratory, his group has pioneered the application of systems biology methods in neurologic and psychiatric disease, with a focus on autism spectrum disorders (ASD) and neurodegenerative conditions. His laboratory has made major contributions to identifying genetic causes of autism spectrum disorder, defining the molecular pathology of autism and allied psychiatric disorders, and has worked to increase diversity in autism research. His work in dementia is focused on the mechanisms of tauopathies, where his laboratory is developing novel therapeutic approaches. He sits on editorial boards of Cell, Science, and Neuron, and is among the highest cited neurologists in the world. He has received several awards for his laboratory's work including the American Neurological Association Derek Denny-Brown Neurological Scholar Award, most recently the Society of Biological Psychiatry Gold Medal Award and the American Academy of Neurology's 2022 Cotzias Lecture and Award, and is an elected Member of the American Association of Physicians and the National Academy of Medicine.

KRISTEN LYALL

Kristen Lyall, Sc.D., is an associate professor at the AJ Drexel Autism Institute at Drexel University. Lyall's research seeks to identify and understand modifiable factors involved in the development of autism-related outcomes. Her work focuses on parental factors, prenatal exposure to environmental chemicals, and maternal dietary factors and their association with child ASD, as well as consideration of ASD-related traits according to continuous, quantitative measures.

KELLY FERGUSON

Kelly Ferguson, Ph.D., M.P.H., leads the Perinatal and Early Life Epidemiology Group and holds a secondary appointment in the NIEHS Reproductive and Developmental Biology Laboratory. The Perinatal and Early Life Epidemiology Group conducts research on how maternal exposure to chemicals impacts pregnancy and the development of the fetus and child. They also investigate inflammation and oxidative stress as biological mechanisms that may connect chemical exposures to adverse birth outcomes. Each research study addresses one or more of the following focus areas: (1) optimal exposure assessment, including examination of chemical mixtures, (2) understanding biologic mediators, (3) outcome phenotyping, and (4) robust validation of associations. Ferguson is specifically trained in chemical exposure assessment, reproductive health endpoints, advanced statistical methods, and epidemiologic study design. She earned her M.P.H. in occupational and environmental epidemiology and Ph.D. in environmental health sciences from the University of Michigan School of Public Health. She joined the NIEHS Epidemiology Branch as a tenure-track investigator in 2016.

ELINOR SULLIVAN

Elinor Sullivan, Ph.D., is an associate professor in the Departments of Psychiatry and Behavioral Neuroscience at Oregon Health & Science University (OHSU) and in the Division of Neuroscience at Oregon National Primate Research Center. Sullivan received her Ph.D. in physiology from OHSU in 2006 and her bachelor's degree in biology from Willamette University in 2000. She received her postdoctoral training at the University of California, San Francisco, and OHSU. Her research focuses on examining the influence of maternal metabolic state and dietary environment on offspring behavioral regulation, with an emphasis on behaviors that relate to mental health and behavioral disorders including autism spectrum disorders, attention deficit hyperactivity disorder, anxiety, and depression. Sullivan is actively involved in training future scientists through her teaching and mentoring of undergraduate and graduate students.

HEHUANG "DAVID" XIE

Hehuang "David" Xie, Ph.D., is a professor at the Department of Biomedical Sciences and Pathobiology, Virginia Tech. The Epigenetics and Computational Laboratory led by Xie combines multidisciplinary approaches to study epigenetic regulatory networks associated with brain development and cell specification. His lab has developed high-throughput techniques to generate large-scale "omics" data. Additionally, the lab has also implemented a number of computational pipelines to perform single cell "omics" data integration. The combined experimental and computational approaches were utilized to understand how the epigenomic/epitranscriptomic aberrations contribute to the effects of maternal diet on the genesis and progression of autism spectrum disorders.

PAUL CURTIN

Paul Curtin, Ph.D., is an assistant professor of biostatistics in the Department of Environmental Medicine and Public Health at the Mount Sinai School of Medicine. His work primarily deals with the exploration of high-dimensional, longitudinal biomarkers of environmental exposure in contexts relating to neurodevelopment. With collaborators, he leads several R01 projects which leverage structural and functional neuroimaging to understand the impact of early life environmental exposures on the developing brain. He recently co-authored Environmental Biodynamics for Oxford Press, which introduces the *Biodynamic Interface Conjecture* and related theoretical perspectives dealing with the interactions of complex systems in environmental epidemiology.

REBECCA SCHMIDT

Rebecca Schmidt, Ph.D., is a tenured associate professor and molecular epidemiologist in the Department of Public Health Sciences and the MIND Institute at the University of California, Davis (UC Davis) School of Medicine. She earned her Ph.D. in epidemiology at the University of Iowa College of Public Health, completed the postdoctoral Autism Research Training Program at the UC Davis MIND Institute, and was a Building Interdisciplinary Research Career in Women's Health scholar. Schmidt aims to advance understanding of how early life environmental exposures interact with genetic susceptibility, molecular mechanisms, and developmental programming to influence neurodevelopmental outcomes of children. Her pioneering work includes finding some of the first evidence in the autism field for a potentially protective effect of folic acid-rich prenatal vitamins, evidence for gene X environment interactions, and protective interactions between folate and environmental contaminants. She co-developed the Early Life Environmental Exposure Assessment Tool. In addition to leading the MARBLES high-risk autism sibling pregnancy cohort study and biorepository, Schmidt leads a wildfire pregnancy cohort study, is site-lead for follow-up of children at older ages in the national ECHO cohort study, and co-leads several mechanistic autism studies, including epidemiologic examinations of mitochondrial, epigenomic, transcriptomic, and metabolomic variations in relation to neurodevelopmental outcomes.

AMANDA MACFARLANE

Amanda MacFarlane, Ph.D., is the founding director of the Agriculture, Food, and Nutrition Scientific Evidence Center at Texas A&M University. She was a research scientist and head of the Micronutrient Research Section at Health Canada from 2008-2022. She is a recognized global leader in nutrition science and nutrition policy. Her research examines the impact of B vitamin nutrition on health and disease spanning from the molecular mechanisms underpinning somatic and germline genome stability to the identification of socioeconomic, dietary, and genetic determinants of B vitamin status at the population level. MacFarlane has also led the development of new tools to assess the risk of bias and quality of nutrition studies. She was the chair of the Canada-U.S. Joint Dietary Reference Intakes (DRIs) Working Group (2013-2022). During that time, she oversaw the formal incorporation of chronic disease endpoints into the DRIs framework, the review of the sodium and potassium DRIs including the first application of the Chronic Disease Risk Reduction values, and the initiation of a review of the macronutrients. She has been actively involved in policy and regulatory work related to food fortification, food labelling, and vitamin supplement content and use. MacFarlane is the member-at-large for the Food and Nutrition Policy of the Board of Directors of the American Society of Nutrition.

EDWIN VAN WIJNGAARDEN

Edwin van Wijngaarden, Ph.D., received an M.S. in environmental sciences from Wageningen University in the Netherlands, and a Ph.D. in epidemiology from the University of North Carolina at Chapel Hill. He is a Fellow of the American College of Epidemiology. Van Wijngaarden is associate chair in the Department of Public Health Sciences. Van Wijngaarden's primary research efforts have focused on the influence of environmental exposures on cognitive outcomes in children and adults. He leads the Seychelles Child Development Study which, for more than 30 years, has investigated the impact of pre- and postnatal methylmercury exposure on child development. Current work includes a NIH-funded infrastructure project which will collect additional data and biological samples needed to continue our integrative and translational science and improve data harmonization and discovery to facilitate data access and sharing.

In addition to conducting primary research, he has significant collaborative research experience in clinical and population health research. Amongst other roles, he co-directs the Clinical and Translational Sciences Institute (CTSI) Biostatistics, Epidemiology, and Research Design key function which provides support and a central source for technical collaboration to investigators for appropriate study design and statistical analysis in clinical and translational science research.

AUDREY GASKINS

Audrey Gaskins, Sc.D., is an assistant professor in the Department of Epidemiology at the Rollins School of Public Health at Emory University. She earned her doctoral degree in nutrition and epidemiology from the Harvard T.H. Chan School of Public Health. This training was preceded by a B.S. in engineering degree from Duke University. As a reproductive epidemiologist, Gaskins has built a strong research portfolio designing and executing studies on the relationship of diet and environmental factors to semen quality, ovarian reserve, fecundability, spontaneous abortion, and infertility treatment outcomes. Gaskins is the principal investigator of two National Institute of Environmental Health-funded grants on exposure to air pollution and early adverse pregnancy outcome with a focus on disentangling sensitive windows of exposure, examining interactions with diet, and elucidating the underlying biological pathways. Gaskins is on the executive board of the Nutrition and Environmental Special Interest Groups of the American Society for Reproductive Medicine and is a methodological editor for Fertility and Sterility.

RACHEL THORNTON

Rachel Thornton, M.D., Ph.D., is vice president and chief health equity officer at Nemours Children's Health where she leads work on health equity strategy to support the organization's vision to create the healthiest generations of children. With hospitals in the Delaware Valley and Central Florida, Nemours Children's Health is one of the largest integrated pediatric health systems in the United States. Thornton has committed her career to health equity research and practice, including organizational transformation.

Prior to joining Nemours Children's, Thornton was associate professor of pediatrics at Johns Hopkins School of Medicine, and the inaugural executive director for clinical services in the Johns Hopkins Medicine Office of Population Health where she led population health management services and community health. A practicing primary care pediatrician, Thornton served as a health policy advisor at the U.S. Department of Housing and Urban Development from 2011-2013. As a nationally recognized innovator in health equity research and practice, she served as a member of the National Academies of Sciences, Engineering, and Medicine study committee on *Shaping Summertime Experiences, Opportunities to Promote Healthy Development and Well-Being for Children and Youth*, and as a member of the Strategy Group on COVID and Rental Evictions.

Thornton received a B.A. from New York University, an M.D. from Johns Hopkins School of Medicine, and a Ph.D. in health policy and management from Johns Hopkins Bloomberg School of Public Health. After residency, she completed fellowship training in general academic pediatrics.

JOSHUA ROFFMAN

Joshua Roffman, M.D., M.M.Sc., is a psychiatrist and neuroscientist who studies the biological underpinnings of serious mental illness (SMI). His longstanding goal has been to develop neuroprotective interventions for SMI through multimodal brain imaging, genomics, and clinical trials. Following work by Roffman and his team that demonstrated neuroprotective effects of folic acid in both schizophrenia and normal brain development, his focus has shifted primarily to prevention. As director of the Early Brain Development Initiative at Mass General, Roffman and his team from Psychiatry, Obstetrics, Pediatrics, and Medicine seek to discover, develop, and implement prenatal and early life protective factors that prevent SMI risk in childhood and adolescence through longitudinal studies of brain development.

Roffman graduated summa cum laude (neuroscience) from Amherst College, followed by medical training at the University of Maryland School of Medicine and the National Institutes of Health. He completed residency and postdoctoral training in the Mass General Department of Psychiatry, where he has remained since 2002. He served as a founding co-director of the hospital-wide Mass General Neuroscience initiative, and currently directs the MGH Division of Psychiatric Neuroimaging. Roffman's research has been supported by the National Institute of Mental Health, Howard Hughes Medical Institute, and the MQ Fellows program. Roffman is associate professor of psychiatry at Harvard Medical School and editor-in-chief of the Harvard Review of Psychiatry.

ANNA MARIA SIEGA-RIZ

Anna Maria Siega-Riz, Ph.D., research focuses on the first 1,000 days of life by understanding the influence of maternal weight status and dietary patterns and behaviors in the etiology of adverse pregnancy outcomes, including, but not limited to, gestational diabetes, pregnancy induced hypertension, pre-eclampsia, preterm birth, and inadequate or excessive gestational weight gain. Her current funded research studies explores the concept of food reward and sensitivity among pregnant women and early determinants of childhood obesity, and the association of maternal preconceptional health with childhood eating and weight status among Hispanics. Other research interests include examining the determinants and consequences of food insecurity and the implications of food policy on health outcomes.

Siega-Riz currently serves on the National Institute of Health's Council of Councils, National Academies of Sciences, Engineering, and Medicine's Health and Medicine Division Advisory Committee, the Food and Nutrition Board, and as a board of trustees member for the International Food Information Council. She is currently chairing the Dietary Reference Intakes for Energy for the National Academy of Medicine, Food, and Nutrition Board. Previously, she served on the 2015 Dietary Guidelines Federal Advisory Committee; the National Heart, Lung, and Blood Institute Advisory Council; the U.S. Department of Agriculture/U.S. Department of Health and Human Services Pregnancy Technical Expert Committee, B–24-month Project; as well as many Institute of Medicine committees. Siega-Riz has received the March of Dimes Agnes Higgins Award for Maternal and Fetal Nutrition; the University of North Carolina Center for Women's Health Research Award for Excellence; and the American Public Health Association, Food, and Nutrition Mary Egan Award. She held key positions at the University of North Carolina at Chapel Hill Gillings School of Global Public Health, including associate dean for Academic Affairs; program leader of the Reproductive, Perinatal, and Pediatric Program in the Department of Epidemiology, and at the University of Virginia as the associate dean for research in the School of Nursing.

Siega-Riz holds a B.S.P.H. from the University of North Carolina Gillings School of Global Public Health, an M.S. in food, nutrition, and food service management from the University of North Carolina at Greensboro, and a Ph.D. in nutrition with a minor in epidemiology from the University of North Carolina Gillings School of Global Public Health. She held the credentials of a registered dietician from 1983–2014.

WEI PERNG

Wei Perng, Ph.D., is an assistant professor of epidemiology in the Department of Epidemiology, and associate director of research training and education for the Lifecourse Epidemiology of Adiposity and Diabetes (LEAD) Center. She is a nutritional and lifecourse epidemiologist whose research focuses on early origins of obesity-related disease, using 'omics technologies as a tool for biomarker assessment, characterizing disease mechanisms, and refining assessment of metabolic phenotypes.

ONYEBUCHI ARAH

Onyebuchi Arah, Ph.D., is an associate dean at the Graduate Division, a professor of epidemiology, and an affiliated professor of statistics at UCLA. He is also Honorary Skou Professor at Aarhus University in Denmark. He is the president-elect of the Society for Epidemiologic Research. His research spans causal inference, quantitative bias analysis, and computational, clinical, and social epidemiology.

JORGE CHAVARRO

Jorge Chavarro, M.D., is professor of nutrition and epidemiology at the Harvard T.H. Chan School of Public Health, and of medicine at Brigham and Women's Hospital and Harvard Medical School. Chavarro's research focuses on understanding how nutritional, lifestyle, and metabolic factors human reproduction and reproductive milestones throughout the life course, and how these events, in turn, impact other aspects of health. Over the last decade, this broad interest has focused primarily on understanding how nutrition impacts human fertility. Chavarro has conducted a variety of studies among healthy individuals and among couples undergoing infertility treatment domestically and abroad. He is principal investigator of the Nurses' Health Study 3, an ongoing prospective cohort study that follows more than 49,000 women. He also leads the nutritional component of the EARTH Study – a prospective cohort of couples undergoing infertility treatment at Massachusetts General Hospital – and of the Young Men's Studies consortium, which studies how the environment influences testicular function by studying young men in Denmark, Spain, and the United States. His work has resulted in more than 300 scientific publications. The American Society for Reproductive Medicine recognized Chavarro's work in 2014 by awarding him the prestigious Ira and Ester Rosenwaks New Investigator Award. He has served as chair of the Nutrition Special Interest Group and the Environment and Reproduction Special Interest Group for this society. He has served in the editorial boards of *Fertility and Sterility, Human Reproduction, Human Reproduction Update*, and Science Advances, and serves as a reviewer of research proposals for the National Institutes of Health and World Health Organization.

YOUSSEF OULHOTE

Youssef Oulhote, Ph.D., received his engineering degree from the National Institute of Veterinary and Agricultural Sciences in Morocco, an M.S. degree in risk assessment from the AgroParisTech Engineering School in Paris, and a Ph.D. from the French National School of Public Health. He worked as a research associate within the Environmental and Occupational Medicine and Epidemiology program at Harvard T. H. Chan School of Public Health where he investigated health effects of chemicals. As an epidemiologist, Oulhote's research focuses on the health effects of early life exposures to metals (e.g., mercury, lead, and manganese) and endocrine disruptors (e.g., PBDEs, PFAS, and phthalates), with an emphasis on children's cognitive and behavioral functions. Oulhote also investigates the application of machine learning techniques within a causal inference framework. Finally, Oulhote's research explores the interplay of environmental, nutritional, and social factors, and how these exposures interact to impact population health.

JOSÉ CORDERO

José Cordero, Ph.D., is the Patel Distinguished Professor of Public Health and head of the Department of Epidemiology and Biostatistics in the College of Public Health at the University of Georgia. He served for 27 years in the U.S. Public Health Service at the Centers for Disease Control and Prevention. His research has focused on improving the health of mothers and children, including folic acid to reduce the risk of neural tube defects, early recognition of autism, and other developmental disabilities. His current research focuses on the role of prenatal environmental exposures to persistent organic pollutants on early neurodevelopment.

JULIE DANIELS

Julie Daniels, Ph.D., completed her doctoral training in epidemiology at the University of North Carolina at Chapel Hill, and her post-doctoral training at the National Institute for Environmental Health Sciences. Her research focuses on prenatal environmental and nutritional exposures that may impact children's growth, neurodevelopment, and overall health. Daniels conducted the Pregnancy, Infection and Nutrition Kids Study to study early life exposure to brominated and organophosphate flame retardants, persistent organic pollutants, and long-chain fatty acids as they relate to children's health. She currently directs the North Carolina site of the Study to Explore Early Development, a multi-site collaborative established to understand the causes and correlates of autism spectrum disorder. This work aims to advance our understanding of how gene expression and environmental exposures interact to alter neurodevelopment. Daniels also studies mental health challenges and service needs that develop among individuals with neurodevelopmental challenges as they age, along with the role social influences play in accessing those services. She values balanced communication of research findings.

ROSALIND WRIGHT

Rosalind Wright, Ph.D., holds the Horace W. Goldsmith Professorship in Children's Health Research, is professor of pediatrics at Mount Sinai Kravis Children's Hospital and Icahn School of Medicine at Mount Sinai, and is Dean for Translational Biomedical Sciences. She received a B.S. in human genetics at the University of Michigan in Ann Arbor, and obtained her medical degree from the University of Michigan Medical School in 1989, graduating cum laude. During medical school, she was selected to spend a year as a Howard Hughes Research Scholar at the National Institutes of Health in Bethesda, Maryland, further pursuing research in molecular biology. Following medical school, Wright completed an internship in internal medicine at the Beth Israel Hospital at Harvard Medical School. She then moved to Chicago, Illinois, to complete her residency in internal medicine at Northwestern University where she also served as chief medical resident. She then returned to Boston to complete fellowship training in Pulmonary and Critical Care Medicine at Harvard Medical School. As part of this training, Wright obtained an M.S.P.H. degree from the Harvard School of Public Health. In 1997, she joined the clinical faculty at the Beth Israel Deaconess Medical Center and the research faculty at the Channing Laboratory, Brigham & Women's Hospital, Harvard Medical School, and the Harvard School of Public Health where she remained on the faculty until she was recruited to Mount Sinai as vice chair of clinical and translational research in the Department of Pediatrics in August 2012.

ANDRES CARDENAS

Andres Cardenas, Ph.D., M.P.H., is an assistant professor in residence in the Division of Environmental Health Sciences at the University of California, Berkeley. Cardenas applies epidemiological and molecular approaches to evaluate the contribution of environmental exposures in the development of disease. He is currently investigating the prenatal influence of exposure to multiple metals, air pollution, endocrine disrupting compounds, diet, and maternal medication use on the epigenome of newborns and children. His current research evaluates the role of environmental exposures in utero, epigenetic modifications, and their role in the developmental origins of health and disease.

Presenter Abstracts

DAN GESCHWIND

KEYNOTE DAY ONE: *The Genetics and Systems Biology of Autism Spectrum Disorder*

Autism Spectrum Disorder (ASD) is a neuropsychiatric condition characterized by the presence of repetitive restrictive behavior and difficulties in social communication and reciprocity. ASD is a syndrome that is it is not defined based on etiology, but rather developmental and medical history, and clinical observations. Although there is high heritability (70-80%), the phenotypic and genetic heterogeneity have challenged efforts to identify causal genetic factors. Nevertheless, the last decade-and-a-half of genetic studies in ASD has yielded substantial advances in our knowledge of its genetic architecture, which is consistent with a significant effect of polygenic risk, as well as substantial contributions from rare de novo variation. Family structure and study design have large influences on the forms of mutations that are identified. For example, whole exome sequencing (WES) studies have identified more than a hundred risk genes, mainly those harboring de novo mutations with large effect sizes, primarily in simplex families (those with only one affected child). By studying families with multiple affected children with ASD (multiplex families), we have been able to show a larger contribution from inherited risk variants, and less of a contribution from de novo variation in multiplex families. By understanding the expression patterns of these risk genes, we can begin to understand which stages of development and in which cell types and circuits ASD risk is acting and determine if there are convergent pathways. Accumulating evidence shows that these genes appear to impact relatively specific molecular pathways and cell types during fetal brain development, providing important clues as to ASD pathophysiology. Similarly, these data indicate that the major risk for ASD is during the mid-fetal period. Thus, environmental factors would be expected to have their largest effect on ASD risk during this time. Knowing this also permits disease modeling, which can incorporate both genetic and environmental contributors. Geschwind's work shows that human IPSC-derived 2D and 3D cultures model human brain development well during the fetal epochs where ASD risk converges, providing a valid platform for understanding mechanisms, as well as screening for the effects of potential environmental risk factors. In addition, to discussing how genetic risk converges during brain development, he discusses some of their efforts in modeling genetic and environmental factors to better understand disease mechanisms.

KRISTEN LYALL

The Role of Maternal Diet and Nutrition in Child Neurodevelopment

Prenatal nutrition is known to play a key role in fetal health and development. The purpose of this talk is to provide an overview of existing evidence supporting a role of maternal dietary factors in relationship to child autism spectrum disorder and related neurodevelopmental outcomes, and to present ongoing findings in this area. Existing work focused on autism has primarily focused on prenatal and periconceptional prenatal and folic acid supplement use, as well as, to a lesser extent, vitamin D and polyunsaturated fatty acids (PUFAs) or fish intake (a key source of PUFAs), with the strongest evidence for an inverse association with folic acid supplement use in early pregnancy and child autism. The role of prenatal dietary intake of other nutrients and dietary factors remain lesser studied. In contrast, a wider set of dietary factors and nutrients have been examined in association with broader neurodevelopmental outcomes, including identification of associations not only with fish, but also dietary patterns, methyl-donor nutrients, and dietary metals, suggesting potential areas to expand autism research. This presentation sets the stage for following talks, while also highlighting areas of need.

KELLY FERGUSON

Oxidative Stress as a Pathway Linking Diet and Child Neurodevelopment: The Promises and the Problems

Maternal oxidative stress levels in pregnancy have been linked to adverse birth outcomes, including preterm birth and preeclampsia, as well as long-term sequelae for the developing fetus. For example, in The Infant Development and the Environment Study (TIDES), urinary 8-isoprostaglandin-F2alpha concentrations from the third trimester of pregnancy were associated with decreased social responsiveness, a measure of severity of autism spectrum symptoms. This same biomarker has been associated with numerous dietary factors in epidemiologic studies. Some dietary components, such as omega-3 fatty acid supplementation, have been associated with lower oxidative stress levels. However, other factors such as selenium, zinc, and copper, which are traditionally considered beneficial, have been associated with higher levels in pregnant populations. A further complication is that oxidative stress levels are strongly associated with sociodemographic factors such as education level and income. Thus, isolating this mechanism in human populations is an ongoing challenge. Future work to investigate dietary factors that influence oxidative stress with careful attention to the confounders that influence biomarker concentrations is needed.

ELINOR SULLIVAN

The Influence of Maternal Nutrition, Metabolic State, and Inflammation on Child Risk for Psychiatric Disorders

In recent decades, the prevalence of pediatric neurodevelopmental disorders, such as autism spectrum disorder and attention-deficit/hyperactivity disorder, have risen dramatically. Mounting evidence indicates a relationship between developmental exposure to maternal obesity, poor nutrition, and increased risk of neurodevelopmental disorders; however, the mechanisms for this association remain unknown. Sullivan's team's work, using non-human primate models, demonstrates causal effects of maternal obesity and poor nutrition on offspring brain development and behavior, specifically increased anxious behaviors and impairments in social behavior. They hypothesize that developmental exposure to maternal obesity and/or poor maternal nutrition alters child behavior and increases risk for neurodevelopmental disorders. They examine this hypothesis in a longitudinal, prospective human study. Sullivan's data support unique effects of maternal adiposity and diet on infant temperament and emotional regulation. Specifically, the researchers find that maternal obesity increases child negative emotions (sadness and fear) and omega-3 fatty acids are protective. New evidence indicates that alterations to the maternal tryptophan-kynurenine pathway during pregnancy could be a mechanistic link between maternal obesity and child behavioral impairments and risk for psychopathology. Lastly, they find evidence that maternal prenatal inflammation may be one common pathway by which prenatal risk factors including obesity, poor nutrition, stress, and depression influence offspring mental health outcomes.

HEHUANG "DAVID" XIE

Functional Links Among Epigenetic Modifications, Maternal Diet, and Autism Risk

The role of maternal folate status in child risk of autism spectrum disorders (ASD) has received great attention and is in debate. While many studies suggest a beneficial effect of higher maternal folate intake against autism, a few studies raised concern about the potential harm of high prenatal folate intake. Xie's team combine the strengths of experimental mouse model with human prospective birth cohort study and transdisciplinary expertise to explore the epigenetic and epitranscriptomic mechanisms underlying the association between maternal folate status and child risk of ASD. Bisulfite sequencing was performed for total RNA and polysome enriched RNA populations to determine folate-associated alterations in transcription and translation. In addition, using single cell RNAseq plus ATACseq technique, they observed the shift in neuronal populations resulted from suboptimal maternal diet indicating the potential harm of folate excess. Their study suggests that optimizing maternal folate levels preconception and during pregnancy holds promise to improve child neuro-developmental outcomes, in addition to other known beneficial health effects.

PAUL CURTIN

Temporal Mechanisms Involved in Metals Dysregulation in Autism Spectrum Disorder

Healthy neurodevelopment requires timely exposure to sufficient essential elements, and the avoidance of toxic elemental exposures. Essential and nonessential metal exposures have traditionally been studied by mapping the toxicological effects of discrete chemicals, following the adage "the dose makes the poison." In recent years, the availability of new biomarker technologies and the emergence of new conceptual paradigms have enabled new insights into the role of these processes in neurodevelopment. This talk will introduce and discuss three new conceptual perspectives for approaching metal dysregulation in autism spectrum disorder. First, the availability of retrospective biomarkers provides new insight into the nature of fetal and early-life exposures, allowing the exploration of time-specific vulnerabilities while simultaneously blurring the traditional distinctions between "nature" and "nurture." Second, the increasing availability of high-resolution longitudinal data will likewise challenge the field to consider the role of endogenous biological processes involved in elemental metabolism. Last, these factors will be discussed in the context of exposomic methodologies which seek to interpret single-chemical effects in the context of complex exposure mixtures. In sum, these frameworks highlight several new avenues for future studies to investigate the role of temporal mechanisms involved in metals dysregulation in autism spectrum disorder.

REBECCA SCHMIDT

State of the Evidence on Nutrient Interactions With Environmental Risk Factors for Autism Spectrum Disorders

Epidemiologic studies provide evidence for associations between nutritional intake and reduced risk for autism spectrum disorder (ASD), as shown for other neurodevelopmental disorders. Nutrients play a role in many pathways that are both involved in neurodevelopment, and have been implicated as potential mediators of increased risk for ASD associated with environmental factors, including DNA methylation and repair, oxidative stress, and inflammation. Evidence for interactions between nutrients and environmental risk factors for ASD is growing. The Childhood Autism Risks from Genetics and the Environment (CHARGE) case-control study found that the highest risk of ASD associated with several types of pesticides was for children whose mothers did not take a prenatal vitamin or supplemental folic acid near conception. Similar interactions were found for traffic-related air pollutants in the CHARGE study, with attenuated risk estimates for ASD in those without prenatal supplements, but no interactions were found for maternal per- and polyfluoroalkyl substances. The Markers of Autism Risk in Babies – Learning the Early Signs (MARBLES) prospective cohort study found greater ASD risk associated with phthalates when mothers did not take prenatal vitamins in the first month of pregnancy, and in the Maternal-Infant Research on Environmental Chemicals (MIREC) pregnancy cohort study, phthalates were associated with greater autistic traits when the mother's prenatal supplemental folic acid intake was <400 mcg. Similar interactions have been observed between prenatal dietary and environmental factors in relation to other neurodevelopmental outcomes, including randomized trials, and some that elucidate potential mechanisms. However, there are many potential explanations for interaction findings, including reporting bias and confounding. Work continues to increase our understanding of relationships between prenatal nutrients, environmental contaminants, ASD, and the mechanistic pathways that could mediate their biological interactions.

AMANDA MACFARLANE

Considerations When Assessing Nutritional Modification of Environmental Exposure - Autism Associations: Examples From B Vitamins and One-Carbon Metabolism

Folate and the other essential B vitamins are required for one-carbon (1C) metabolism. Folate-mediated 1C metabolism is required for the de novo synthesis of purines, thymidylate, and methionine that, in turn, support DNA synthesis and cellular methylation potential. Altered 1C metabolism due to genetic polymorphisms and variable dietary intake can result in DNA mutagenesis, chromosomal instability, and altered cellular methylation with implications for cell proliferation and gene expression. This presentation provides an overview of 1C metabolism, its association with autism risk, and how it might modify the associations between environmental exposure(s) and autism. MacFarlane highlights a number of important considerations related to study design, including nutrition exposure assessment that may explain some of the heterogeneity observed in studies examining these associations.

EDWIN VAN WIJNGAARDEN

The Influence of Methylmercury Exposure and Nutrients on Neurodevelopmental and Neurobehavioral Outcomes in High Fish Consumers: Results From the Seychelles Child Development Study

Fish are a primary source of daily nutrition for billions of people around the world and provide nutrients essential for normal brain development. All fish also contain small amounts of naturally-acquired methylmercury (MeHg), and low-level prenatal MeHg exposure from fish consumption is universal. MeHg is known to be a developmental neurotoxicant at high exposures associated with poisoning episodes, but epidemiologic studies have been conflicting regarding the impact of low-level MeHg exposures. The known benefits of eating fish versus the potential toxicity of low-level MeHg exposure has made it challenging to formulate fish consumption advice for pregnant women. The Seychelles Child Development Study began in the mid-1980s to examine the association between prenatal exposure and neurodevelopmental outcomes to clarify the risks associated with low-level MeHg exposure from eating fish. The Republic of Seychelles was selected as a study location because fish consumption in the islands is high and the average MeHg exposure in Seychelles is about 10 times that of the U.S. population. We have investigated the impact of prenatal MeHg exposure on child neurodevelopment in three NIH-funded longitudinal mother-child cohorts: the Main cohort (recruited 1989-1990), the first Nutrition cohort (NC1, recruited 2001), and the second Nutrition cohort (NC2, recruited 2008-2011). These studies have made important contributions to our understanding of possible low-level MeHg neurotoxicity. Wijngaarden's team's findings suggest that nutrients in fish, in particular n-3 long-chain polyunsaturated fatty acids (PUFA), are beneficial for child development and could mask MeHg toxicity. Wijngaarden also found that there may be an optimal balance between the different types of PUFA that plays a critical role in influencing MeHg developmental toxicity. They have studied underlying mechanisms to explain these findings through genetic studies and assessment of markers of immune function, mitochondrial homeostasis, and DNA methylation. Their findings indicate that genes on the glutathione axis influence the metabolism of MeHg, and that genes associated with PUFA metabolism influence serum PUFA concentrations. Finally, their data suggest that prenatal MeHg exposure and PUFA may influence intermediate biomarkers of effect, some of which have, in turn, been associated with neurodevelopmental and neurobehavioral outcomes.

AUDREY GASKINS

Diet as a Modifier of Air Pollution Exposure: Integrating Evidence From Other Reproductive Endpoints

Increasing evidence suggests that air pollution, a ubiquitous environmental exposure, is related to lower human fertility, increased risk of many adverse pregnancy outcomes, and higher risk of certain birth defects. On the other hand, an adequate periconceptional nutrition status is considered a key determinant of many of these same outcomes in women and could potentially reduce the toxicity of environmental pollutants. Folic acid is a nutrient of primary interest given the substantial literature relating it to improved reproductive and pregnancy outcomes in women, and a growing literature suggesting that it may attenuate the effects of reproductive toxicants such as bisphenols, phthalates, pesticides, and arsenic. Emerging evidence also suggests that folic acid may attenuate the relationship between air pollution and reproductive outcomes such as birth defects, autism, and, most recently, fertility. Although the specific underlying biological pathways through which air pollution and folic acid interact to affect reproductive endpoints are unknown, epigenetic mechanisms, including alterations in DNA methylation of the oocyte, are of primary interest. This could also potentially explain the consistency in association across endpoints, as alterations in oocyte methylation confers a double risk of compromising the reproduction capacity of the exposed individual and transmitting possible damage to the following generation.

RACHEL THORNTON

Putting Research Findings Into Context: What Do We Learn From the Legacy of Health Equity Research?

Environmental conditions and the social forces that produce them are not randomly distributed across populations. This presentation provides insights from health equity and health disparities research about the mechanisms by which social conditions may contribute to consistent patterns of health and illness within society. While the examples draw from outside environmental health sciences, the presentation expands the frame through which researchers should consider social forces as potential confounders or common antecedents that drive childhood neurodevelopmental outcomes. What do we miss when we examine the association of environmental factors with neurodevelopmental outcomes without considering social forces? How can evaluation of social forces such as segregation, opportunity, racial stratification, poverty, or systemic inequities in research examine links between environmental toxins and disease outcomes? What implications would a focus on common social forces have for prevention, treatment, or intervention development? Intended to raise more questions than answers and spur innovation, this presentation widens the aperture through which we view linkages between environmental exposures and child neurodevelopment.

JOSHUA ROFFMAN

KEYNOTE DAY TWO: ***Neuroprotective Effects of Prenatal Folic Acid Across Cells, Circuits, and Society***

Periconceptional folic acid is one of the first candidate interventions for primary prevention in psychiatry, with replicated data demonstrating substantial mitigation of autism risk. This presentation describes ongoing efforts to understand intermediate mechanisms of these effects, and to optimize uptake of periconceptional acid across diverse populations. First, using human induced pluripotent stem cell models, we have demonstrated that pre-treatment with folic acid mitigates effects of maternal immune activation on developing pyramidal neurons. This approach is now being broadened to study folate's effects on cell-specific gene expression in three-dimensional brain organoid models of human brain development. Next, using brain imaging data from replicated adolescent cohorts, we demonstrated effects of increased periconceptional folic acid exposure on cortical maturation and related psychotic symptoms – a finding that is now being extended to include advanced MRI studies of synaptic pruning and intracortical myelination. Moving next to clinical translation, ongoing work to understand persistent provider- and patient-level implementation gaps in periconceptional folic acid uptake will be described, as part of an effort to leverage these neuroscientific insights into improved brain health outcomes among diverse populations of youth. Roffman concludes by describing opportunities afforded by large-scale longitudinal cohort studies, such as the ongoing Adolescent Brain Cognitive Development Study and the new HEALthy Brain and Child Development Study, to model effects of prenatal and early life environmental exposures on the developing brain, from preconception to late adolescence. Thus, using periconceptional folic acid as an example, this presentation illustrates how a range of translational neuroscience platforms can be deployed to model effects of environmental exposures on early brain development, with the ultimate goal of developing new strategies for prevention and early intervention.

ANNA MARIA SIEGA-RIZ

Methods for Assessing Dietary Intake During the Periconceptional Period and Nutritional Epidemiological Approaches for Examining Diet-Disease Relationships

This presentation provides an overview of current and forthcoming dietary assessment methods used during the periconception period. The complexity of measuring intake from examining dietary patterns to specific nutrients will be discussed. Emphasis is placed on understanding individual variability and the interconnection with genetics and environmental factors as the field moves toward precision nutrition and understanding etiology of various early childhood conditions such as ASD.

WEI PERNG

You Are What You Eat…and Metabolize: Biomarkers of Dietary Intake and How Metabolomics Can Help

Assessment of dietary intake is a compromise between data quality and methodological feasibility, often resulting in threats to accuracy, reliability, and/or validity. Biochemical markers measured in tissues ("biomarkers") can serve as objective proxies for dietary intake. This presentation provides a brief overview of dietary assessment methods with a focus on dietary biomarkers, and discusses metabolomics as a tool for biomarker discovery and dietary assessment in the field of nutritional epidemiology.

ONYEBUCHI ARAH

Methods for Effect Modification, Interaction, and Mediation

This presentation discusses modern methods from the causal inference literature that can be used to study how nutrition or diet mediates, interacts with, and modifies the effects of environmental exposures on autism spectrum disorder (ASD). It will showcase augmented causal diagrams to depict individual versus joint exposure effects, clearly specified research questions and related estimands, conditions for identifying effects, estimation methods, and quantitative bias analysis. This presentation concludes with a note on transparency and triangulation when investigating nutritional factors as effect modifiers, secondary exposures, or mediators in the mechanisms linking environmental exposures to ASD.

JORGE CHAVARRO

Evaluating Health Effects of Environmental Exposures When Diet Is the Route of Exposure: The Example of Pesticide Residues in Food

Increasing evidence suggests that some nutrients may mitigate the health effects of environmental exposures. Nevertheless, foods rich in potentially beneficial nutrients may themselves be the main exposure source of potentially hazardous environmental exposures. The ability to differentiate between the (putatively positive) nutritional effects of a food or food group from the (putatively negative) effects of environmental exposures a food or food group serves as a vehicle for, is a critical issue sitting at the intersection of nutritional and environmental health sciences with major implications for etiologic research and the development of public health guidance. This presentation describes how collaboration between nutritional and environmental health scientists led to the development of a method to assess pesticide residues in fruits and vegetables for use in epidemiologic studies, the strengths and weaknesses of this approach, and how similar methods could be used to address related questions.